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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/009,134	10/20/2002	Chandrasekhar Satishchandran	AM100013	5538

25291 7590 03/08/2007

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EXAMINER	
CHONG, KIMBERLY	
ART UNIT	PAPER NUMBER
1635	

SHORTENED STATUTORY PERIOD OF RESPONSE	MAIL DATE	DELIVERY MODE
3 MONTHS	03/08/2007	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

If NO period for reply is specified above, the maximum statutory period will apply and will expire 6 MONTHS from the mailing date of this communication.

Office Action Summary	Application No.	Applicant(s)	
	10/009,134	SATISHCHANDRAN ET AL.	
	Examiner	Art Unit	
	Kimberly Chong	1635	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *07 December 2006*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *107-168 and 171-173* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *107-168, 171-173* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Status of Application/Amendment/Claims

Applicant's response filed 12/07/2006 has been considered. Rejections and/or objections not reiterated from the previous office action mailed 08/07/2006 are hereby withdrawn. The following rejections and/or objections are either newly applied or are reiterated and are the only rejections and/or objections presently applied to the instant application.

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Claims 68-173 are pending. Claims 107-168 and 171-173 are currently under examination. Claims 68-106 and 169-170 are withdrawn as being drawn to a non-elected invention.

Priority

Claims 107-138, 140-168 and 171-173 of the instant application are accorded the priority date of 04/19/2000.

Claim 139 is accorded a priority date of 10/02/2002, the filing date of the instant application, for the reasons stated in the new matter rejection below.

New Claim Rejections

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claim 139 is rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. This is a new matter rejection.

Claim 139 is drawn to an expression vector wherein said vector encode two or more different double stranded sequences wherein each different double stranded RNA sequences comprise at least 11 to 30 nucleotides involved in the double stranded sequence. Claim 139 embraces an expression vector that encodes two or more double stranded sequences each comprising *only* 11-30 nucleotides in length.

The specification on page 17, lines 16-17 disclose the RNA molecule can be complete or partially double stranded and on page 20, lines 7-16, the specification discloses expression vectors designed to produce said RNA as described. Additionally the specification discloses the entire sequence of the RNA molecule can be double stranded, however the specification discloses the RNA polynucleotide sequence is 100 to 10,000 polynucleotides in length and more desirable at least 200 nucleotides.

Therefore, while the entire RNA sequence can be double stranded, this RNA polynucleotide is disclosed to be at a minimum 100 nucleotides in length.

The specification does not contemplate an expression vector wherein said vector encodes two or more different double stranded sequences wherein each different double stranded RNA sequences comprise only 11 to 30 nucleotides involved in the double stranded sequence.

If Applicant believes the prior applications provide support then applicant must point, with particularity, to where such support can be found in the specification of the prior applications.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.

Claim 139 is rejected under 35 U.S.C. 102(a) as being anticipated by Leirdal et al. (cited on PTO Form 892 filed 08/07/2006).

Claim 139 is drawn to an expression vector wherein said vector encode two or more different double stranded sequences wherein each different double stranded RNA sequences comprise at least 11 to 30 nucleotides involved in the double stranded sequence.

Leirdal et al. teach a multitarget partially double stranded RNA molecule comprising two different double stranded RNA sequences that are complementary to a GFPsi1 sequence and a PKCαsi3 sequence which is responsible for apoptosis in glioma cells (see Figure 1 and page 747). Leirdal et al. teach the partially double stranded RNA molecule comprises a single stranded region that is a cleavage site for endoribonuclease (see column 1, page 746). Leirdal et al. teach the partially double stranded sequence is transcribed in vitro by a DNA template comprising a T7 promoter and teach a pEGFP-N3 expression vector for expression of GFP and additionally teach the use of expression vectors comprising pol III promoters such as U6 for efficient expression of double stranded RNA (see column 1, page 744 and page 747).

Thus, Leirdal et al. anticipates claim 139 of the instant application.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 107-168 and 171-173 are rejected under 35 U.S.C. 103(a) as being unpatentable over Werther et al. (cited on PTO Form 892 filed 08/07/2006), Fire et al. (cited on PTO Form 892 filed 08/07/2006), Heifetz et al (cited on PTO Form 892 filed

08/07/2006); Calabretta et al. (US Patent No. 5,734,039) and Thompson et al. (cited on PTO Form 892 filed 08/07/2006).

The instant claims are drawn to a multitarget partially double-stranded RNA molecule comprising two or more different double stranded RNA sequences that are substantially homologous and complementary to two or more sequences of at least one target gene or substantially homologous and complementary to two or more sequences of more than one target gene, wherein at least 11 to 30 nucleotides are involved in the double stranded RNA molecule, wherein said double stranded region comprises at least 50% homology to a target gene, wherein said partially double stranded RNA molecule is between 100 to 10,000 polynucleotides in length, wherein said double stranded region comprises a sense and antisense separated by a non-base paired polynucleotide region and is separated by cleavage sequences, wherein the target gene is from a pathogen such as a virus, wherein the target gene is associated with a disease in a mammal such as a cancer associated gene, wherein the target gene is selected from a transcribed, non-transcribed, coding, non-coding, exon-containing, regulatory or promoter sequence, wherein the double stranded region lacks a polyadenylation signal, wherein a composition comprises said RNA, wherein a DNA molecule encodes said RNA, wherein an expression vector encodes said RNA, wherein said RNA is expressed using a promoter and wherein said vector is plasmid, phage or recombinant vector. The instant claims are further drawn to an expression vector encoding two or more different double stranded RNA sequences that are substantially homologous and complementary to two or more sequences of at least one target gene, wherein at least 11 to 30 nucleotides are

involved in the double stranded RNA molecule, wherein said double stranded region comprises at least 50% homology to a target gene, wherein said double stranded region comprises a sense and antisense separated by a non-base paired polynucleotide region, is a hairpin RNA and is separated by cleavage sequences, wherein said RNA sequences are expressed using a promoter or two or more different promoters, wherein said vector is plasmid, phage or recombinant vector, wherein the target gene is from a pathogen such as a virus, wherein the target gene is associated with a disease in a mammal such as a cancer associated gene, wherein the target gene is selected from a transcribed, non-transcribed, coding, non-coding, exon-containing, regulatory or promoter sequence, wherein the double stranded region lacks a polyadenylation signal and wherein a composition comprises said RNA.

Werther et al. teach a multivalent antisense molecule targeted to two sequences of a target gene IGFBP or targeted to two or more sequences in different target genes such as IGFBP-2 and IGFBP-3 (see column 3). Werther et al. does not each a partially double stranded RNA comprising two or more different double stranded RNA sequence that are complementary to two or more sequence of at least one target gene. Werther et al. does not expression of said double stranded RNA from an expression vector wherein said expression vector expresses two different double stranded RNA sequences using two promoters.

Calabretta et al. teach a multivalent antisense molecule targeted to two sequences of cooperating oncogenes and teach vectors for expression of each said

antisense molecules under the control of a corresponding first and second promoter (see column 19, lines 50-63).

Fire et al. teach double stranded RNA wherein the duplex regions of the RNA are capable of hybridizing with the target gene wherein the length of the duplex regions are from 25 to 400 bases (see columns 7-8). Fire et al. teach expression vectors comprising T7 polymerase promoters and teach the target gene may be derived from any cell of any organism wherein the organism may be a plant, animal or human (see column 8, lines 12-20). Fire et al. additionally teach the target gene may derived from any pathogen or any cell already infected by a pathogen such as HIV for example (see column 10, lines 8-18). Fire et al. teach the use of double stranded RNA for RNA inference is an effective alternative to antisense methodologies.

Heifetz et al. teach production of a double stranded interfering RNA comprising introducing into plant cells DNA sequences encoding a sense RNA strand and an antisense RNA strand into an expression vector wherein the sense and antisense RNA strands are complementary to each other and form a double stranded RNA (see page 8). Heifetz et al. teach the complementary regions can be 15, 50 or 500 nucleotides in length (see page 11). Heifetz et al. teach the DNA sequences are preferably operably linked to one or more promoters wherein the promoter is a heterologous promoter (see page 10 last paragraph to the top of page 11). Heifetz et al. teach the DNA sequences that form the double stranded RNA are inserted into the same vector wherein the sequences encodes a sense and an antisense strand or the DNA sequences that encode a sense strand or an antisense strand are in separate vectors (see pages 8-9).

Heifetz et al. teach viral vectors can be used to introduce the DNA molecules into the plant cells (see page 11) and further teach methods of altering the expression of a target gene by introducing a vector comprising said DNA sequences as stated above (see pages 12-13 and Examples 1 and 3).

It would have been obvious to one of skill in the art to make a multitargeted double stranded RNA wherein said double stranded RNA targets at least one or more than one target gene and further it would have been obvious to use expression vectors comprising two promoters for expressing said dsRNAs.

One would have been motivated to make a multitargeted double stranded RNA targeted to two or more sequences of at least one target gene because certain target sequences are capable of mutation and targeting multiple sites on a target gene is advantages for effective therapeutics. Further, one would have been motivated because certain diseases are triggered by expression from similar genes and therefore inhibition of multiple genes, as taught by Werther et al. is an effective method. Additionally, Calabretta et al. teach simultaneous targeting of genes using two antisense compounds is advantageous to inhibit expression of cooperating oncogenes responsible for cancer and therefore the skilled artisan would have clearly been motivated to express dsRNA using different promoter for efficient expression of each dsRNA targeted to a target gene for the purpose of inhibiting gene expression. One would have been motivated to use double stranded RNA because Fire et al. teach double stranded RNA capable of initiating RNA interference is more sequence specific alternative to reducing expression of a target gene than antisense type mechanisms

(see columns 1-3). One would have had a reasonable expectation of success given that Werther et al. teach construction of multitarget antisense and Fire et al. and Heifetz et al. teach gene inhibition using double stranded RNA wherein said duplex region is complementary to said target gene and wherein said double stranded RNA is expressed using an expression vector comprising one or more promoters.

Werther et al., Fire et al. Heifetz et al. and Calabretta et al. do not teach an expression vector comprising a RNA pol III promoter.

Thompson teaches expression of therapeutic RNAs such as ribozymes and antisense RNA using RNA pol III based expression cassettes (see column 4, lines 11-20). Thompson teaches that in order for therapeutic RNAs to be effective, sufficient amounts must accumulate in the appropriate intracellular compartments (see column 10, lines 18-25). Thompson further teach pol III based expression cassettes are more attractive for expressing RNAs because pol III produces functional RNAs found in both the nucleus and the cytoplasm, are likely to be expressed in all tissue types and accumulate to much greater levels in cells (see column 10, lines 27-39). Thompson teach these advantages of pol III expression cassettes are desired for expressing RNAs *in vivo* and more particularly antiviral RNAs *in vivo* (see column 10, lines 41-50). Thompson further teach production and accumulation of RNA transcripts produced from a pol III expression cassette in human 293 cells (see column 15 line 55 to column 16 line 9).

One of skill in the art would have been motivated to incorporate a RNA pol III promoter into the expression vector since Thompson teach pol III promoters are more

attractive for expression of RNAs in all tissue types and the accumulation in the cells is greater from a pol III based expression vector. Moreover, both Heifetz et al. and Fire et al. teach expression vectors used for producing double stranded interfering RNA can comprise different promoters and Heifetz et al. specifically teach that promoters vary in their ability to promote transcription and one of skill in the art would choose a suitable promoter depending on the host cell system utilized (see page 15). Therefore, one would be motivated to use a pol III promoter for expression in mammalian cells, as taught by Thompson.

Thus, in absence of evidence to the contrary, the invention as a whole would have been *prima facie* obvious to one of skill in the art at the time the invention was made.

The foregoing represents a new rejection; however Applicants arguments will be responded to since portions of the arguments are considered relevant to the rejection as newly stated. Applicant argues the skilled artisan would not have been motivated to substitute a double stranded region that is both homologous and complementary to a target gene into a multivalent antisense molecule because then the "...antisense regions of Werther's multivalent molecule would no longer be free to bind to the target transcripts."

At the outset, it is unclear what is meant in applicant's arguments regarding substituting "regions" of an antisense compound with dsRNA regions. Werther et al. teach a multitargeted antisense compound targeted to two sequences of a target gene

IGFBP and demonstrates effective gene inhibition and one would have been motivated to make a multitarget double stranded RNA in general targeted to two or more sequences of at least one target gene because certain target sequences are capable of mutation and targeting multiple sites on a target gene is advantages for effective therapeutics because dsRNA have been shown to be more potent than antisense compounds. The 103 rejection of record filed 08/07/2006 discusses the motivation of the skilled artisan to use the invention of multitargeted antisense compounds to make multitargeted dsRNA for the effective silencing of gene expression.

Applicants further argue that in constructing a proper obviousness rejection, the proposed modification introduced by the secondary reference cannot change the principal mode of operation and because the only mechanism disclosed in Werther et al. for inhibiting gene expression is antisense inhibition, there would have been no motivation to use a dsRNA. This argument is not convincing. Both the antisense compounds taught by Werther et al. and the dsRNA taught by Fire and Heifetz et al. operate to inhibit gene expression and despite the different mechanisms of action, both molecules are considered inhibitory molecules. One of skill in the art would have clearly understood the mechanisms were different but the outcome is the same and because Werther et al. teach efficient inhibition of gene expression using antisense compounds targeted to different genes and teach this method of targeting different genes using more than one antisense molecule is efficient in the treatment of diseases, the skilled artisan would have been motivated to a make a multitargeted dsRNA to target different

genes for silencing of gene expression of multiple genes responsible for certain diseases.

Lastly, applicants argue they fail to understand examiners point about "co-suppression". It is clear from the context of the paragraph that co-suppression, while not technically correct as alleged by applicant, is referring to inhibiting gene expression of multiple genes simultaneously.

Thus, as stated in the rejection above, the invention, as a whole would have been *prima facie* obvious to one of skill in the art at the time the invention was made.

Re: Claim Rejections - 35 USC § 103

Applicants arguments for the rejection of record of claims 107-148, 156-168 and 171-173 under 35 U.S.C. 103(a) as being unpatentable over Taira et al. (cited on PTO Form 892 filed 11/22/2005) and Fire et al. (US Patent No. 6,506,559) is obviated as the rejection of record filed 08/07/2006 is withdrawn.

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Kimberly Chong whose telephone number is 571-272-3111. The examiner can normally be reached Monday thru Friday between 7-4 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, James Schultz can be reached at 571-272-0763. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Patent applicants with problems or questions regarding electronic images that can be viewed in the Patent Application Information Retrieval system (PAIR) can now contact the USPTO's Patent Electronic Business Center (Patent EBC) for assistance. Representatives are available to answer your questions daily from 6 am to midnight (EST). The toll free number is (866) 217-9197. When calling please have your application serial or patent number, the type of document you are having an image problem with, the number of pages and the specific nature of the problem. The Patent Electronic Business Center will notify applicants of the resolution of the problem within 5-7 business days. Applicants can also check PAIR to confirm that the problem has been corrected. The USPTO's Patent Electronic Business Center is a complete service center supporting all patent business on the Internet. The USPTO's PAIR system provides Internet-based access to patent application status and history information. It also enables applicants to view the scanned images of their own application file folder(s) as well as general patent information available to the public. For more information about the PAIR system, see http://pair-direct.uspto.gov.

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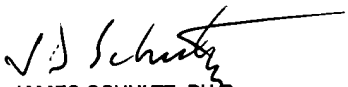

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